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DOI:

[10.1016/j.resp.2015.11.006](https://doi.org/10.1016/j.resp.2015.11.006)

Document Version

Peer reviewed version

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Citation for published version (APA):

Lunt, A., McGhee, E., Robinson, P., Rees, D., Height, S., & Greenough, A. (2016). Lung function, transfusion, pulmonary capillary blood volume and sickle cell disease. *RESPIRATORY PHYSIOLOGY AND NEUROBIOLOGY*, 222, 6-10. <https://doi.org/10.1016/j.resp.2015.11.006>

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HIGHLIGHTS

- Obstructive and restrictive lung function abnormalities occur in SCD children
- SCD children have increased pulmonary capillary blood volume (PCBV)
- Respiratory system resistance and PCBV were measured before/after transfusion
- Respiratory system resistance and PCBV significantly increased post transfusion
- Increased PCBV may partially explain lung function abnormalities in SCD children

ABSTRACT

Lung function abnormalities occur in children with sickle cell disease (SCD) and may be associated with elevated pulmonary blood volume. To investigate that association, we determined whether blood transfusion in SCD children acutely increased pulmonary capillary blood volume (PCBV) and increased respiratory system resistance (Rrs5). Measurements of Rrs5 and spirometry were made before and after blood transfusion in 18 children, median age 14.2 (6.6 – 18.5) years. Diffusing capacity for carbon monoxide and nitric oxide were assessed to calculate the PCBV. Post transfusion, the median Rrs5 had increased from 127.4 to 141.3% predicted ($p < 0.0001$) and pulmonary capillary blood volume from 39.7 to 64.1 ml/m₂ ($p < 0.0001$); forced expiratory volume in one second ($p=0.0056$) and vital capacity ($p=0.0008$) decreased. The increase in Rrs5 correlated with the increase in PCBV ($r=0.50$, $p=0.0493$). Increased pulmonary capillary blood volume may at least partially explain the lung function abnormalities in SCD children.

Key words: Sickle cell disease, lung function abnormalities, pulmonary capillary blood volume, transfusion

Lung function, transfusion, pulmonary capillary blood volume and sickle cell disease

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ABSTRACT

Lung function abnormalities occur in children with sickle cell disease (SCD) and may be associated with elevated pulmonary blood volume. To investigate that association, we determined whether blood transfusion in SCD children acutely increased pulmonary capillary blood volume (PCBV) and increased respiratory system resistance (Rrs5). Measurements of Rrs5 and spirometry were made before and after blood transfusion in 18 children, median age 14.2 (6.6 – 18.5) years. Diffusing capacity for carbon monoxide and nitric oxide were assessed to calculate the PCBV. Post transfusion, the median Rrs5 had increased from 127.4 to 141.3% predicted ($p < 0.0001$) and pulmonary capillary blood volume from 39.7 to 64.1 ml/m₂ ($p < 0.0001$); forced expiratory volume in one second ($p=0.0056$) and vital capacity ($p=0.0008$) decreased. The increase in Rrs5 correlated with the increase in PCBV ($r=0.50$, $p=0.0493$). Increased pulmonary capillary blood volume may at least partially explain the lung function abnormalities in SCD children.

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1. INTRODUCTION

Sickle cell disease (SCD) is one of the commonest inherited disorders worldwide; approximately 250,000 children are born with homozygous SCD per year (Piel et al 2013). The majority of children with SCD in developed countries can expect to survive to adulthood [Quinn et al 2010], but may then suffer severe pulmonary morbidity including hypoxia and pulmonary hypertension (Powars et al 1988). Restrictive and obstructive lung function abnormalities are common. Restrictive lung disease is associated with increasing age (Sylvester et al. 2004, MacLean et al. 2008) and obstructive defects can occur even in young children with SCD (Koumbourlis et al 2001, 1997). Hence, it is important to understand the etiology of such abnormalities; mechanistic insights are necessary to better inform therapy to hopefully prevent SCD pulmonary complications. A number of researchers have suggested that asthma is responsible for impaired lung function and respiratory symptoms in SCD, but the evidence is conflicting. A high prevalence of asthma in children with SCD has been reported in one study (Knight-Madden et al 2005), but not in others (Bernaudin et al 2008, Boyd et al 2004). In addition, the response to bronchial challenges in SCD patients, such as cold air, exercise, or methacholine has been variable ranging from no response (Chaudry et al 2014) to 78% of those tested having a positive response (Ozbek et al 2007). Furthermore, whereas some studies have shown a high response rate to bronchodilator therapy in SCD children compared to controls (Knight-Madden et al 2005, Koumbourlis et al 2001), others have shown no significant difference in the response rates of SCD children compared to that of controls (Sylvester et al 2004).

An alternative explanation for the impaired lung function is increased pulmonary capillary blood volume due to chronic anemia resulting in a raised cardiac output and increased vascular recruitment and distension (Batra et al 2002, Chaudry et al 2011, Delclaux et al 2005, Femi-Pearse et al 1970, Lunt et al 2014, Wedderburn et al 2014). Indeed, we have demonstrated children with SCD have increased pulmonary capillary blood volume

compared to controls, which was associated with airway obstruction and correlated with respiratory system resistance (Wedderburn et al 2014). Similarly in adults, vascular changes on high resolution computed tomography (HRCT) (increased segmental pulmonary artery diameter and total cross-sectional area of all pulmonary vessels less than 5mm in diameter (CSA<5mm%), correlated with reductions in lung function (Lunt et al 2014). Experimental increases in thoracic blood volume have been shown to produce reductions in lung function and an increase in respiratory system resistance. For example, rapid saline infusion has been shown to produce a significant decrease in dynamic lung volumes as assessed by spirometry in healthy adults (Collins et al 1973, Muir et al 1975), as well as in patients with left ventricular failure (Puri et al 1999). In addition, Lorino et al found that the inflation of pneumatic trousers in healthy subjects caused an increase in respiratory system resistance as assessed by impulse oscillometry (Lorino et al 1994). Recently Bihari et al (2015) demonstrated that in healthy subjects, infusion of 0.9% saline caused a significant increase in respiratory system resistance at 5Hz as assessed by impulse oscillometry. Such studies have not been performed in SCD children, but some SCD children receive blood transfusions as part of their routine care. Blood transfusions have been shown to result in transient increases in cardiac output (Duke et al 1964). Routine blood transfusions in SCD children would then allow investigation of the acute effect of fluid loading on lung function and further add to the understanding of the etiology of pulmonary function impairment in SCD children. The aim, therefore, of this study was to test the hypothesis that blood transfusion would result in an acute increases in pulmonary capillary blood volume and respiratory system resistance and reductions in spirometry in children with SCD. Such data would further aid the understanding of the pathophysiology of lung function abnormalities in SCD children.

2. METHODS

Children homozygous for sickle cell haemoglobin (HbSS) undergoing regular blood transfusion at King's College Hospital NHS Foundation Trust, London were recruited. Only children of seven years of age or greater were recruited as they were likely to be able to complete all the lung function tests. The study was approved by the King's College Hospital NHS Foundation Trust Research Ethics Committee and parents gave informed, written consent for their child to take part. Impulse oscillometry, spirometry and pulmonary capillary blood volume were measured before and immediately after transfusion. In order to further characterise the lung function of the patients, static lung volumes were measured before transfusion. The volume of packed red cells (PRCV) administered to each patient was determined using the following formula: $\text{PRCV (mls)} = \text{patient weight (kg)} * \text{change in haemoglobin to be achieved (g/dl)} * \text{transfusion factor of (4-5 ml.kg}^{-1}\text{/g.dl}^{-1}\text{)}$, in order to achieve a target haemoglobin concentration of 13.5g/dl. All transfusions were administered over approximately four hours.

2.1 Lung function assessments

Spirometry, gas transfer for carbon monoxide and body plethysmography were performed. The forced expiratory volume in one second (FEV_1) vital capacity (VC), ratio of FEV_1 to VC (FEV_1/VC), forced expiratory flow between 25 and 75% of VC (FEF_{25-75}), transfer factor for carbon monoxide (DLCO), transfer factor adjusted for alveolar volume (KCO), total lung capacity (TLC), residual volume (RV) and the ratio of RV to TLC (RV:TLC) were assessed according to ATS/ERS guidelines. The highest forced vital capacity result obtained from spirometry and the slow vital capacity from the DLCO manoeuvre were reported as VC. Results were expressed as the percentage predicted for height using an ethnic-specific reference range for spirometry and Caucasian reference data for gas transfer and body plethysmography (Quanjer et al 2012, Rosenthal et al 1993). Respiratory system resistance

(Rrs) was also measured using impulse oscillometry. R_{rs} was measured before the other lung function tests and a resistance at 5 Hz (Rrs5) was used in order to assess both distal and proximal changes in lung function. Respiratory system resistance at 20Hz (Rrs20), the frequency dependence of resistance (R5-R20), the respiratory system reactance at 5Hz (Xrs5), the resonant frequency (f_{res}) and the area under the reactance curve between resonant frequency and 5Hz (AX) were also recorded. For all IOS indices the whole-breath values were reported. All measurements were performed using a commercially available lung function system (Jaeger MasterScreen IOS, Carefusion Ltd, Basingstoke UK).

The Rrs5, Rrs20, Xrs5, and f_{res} results were expressed as the percent predicted for height using the reference range of Nowowiejska *et al* (Nowowiejska *et al* 2008). Raw values were reported for R5-R20 and AX as predicted values are not available for these indices for the age range of the children studied. For IOS indices, the mean of two measurements for Rrs5 and Rrs20 were reported for each measurement the two results were within 5% of each other.

Patients were diagnosed with an obstructive abnormality if their FEV1:FVC was less than the lower limit of normal (LLN) (Pellegrino *et al* 2005), based on the ethnic specific reference range of Quanjer *et al*. A restrictive abnormality was diagnosed if the TLC was below the LLN (Pellegrino *et al* 2005) based on the reference range of Rosenthal *et al*, with a -12% correction factor applied (Kirkby *et al* 2013). A mixed abnormality was diagnosed if the TLC and FEV₁/VC were less than the LLNs (Pellegrino *et al* 2005).

2.2 Pulmonary capillary blood volume

Pulmonary capillary blood volume was measured using the single breath-hold method for gas transfer for carbon monoxide (DLCO) and nitric oxide (DLNO) using a commercially available system (Jaeger MasterScreen PFT Pro, Carefusion Ltd, Basingstoke UK)

Pulmonary membrane diffusing capacity (DMCO) and pulmonary capillary blood volume (PCBV) were determined using the Roughton-Forster model as previously described (Wedderburn et al 2014). PCBV was 'normalised' to estimated body surface area (BSA) using the formula of Mosteller et al (Mosteller 1987). The mean of two measurements within 5% was reported. Baseline DLCO results corrected for the haemoglobin concentration [Hb] from a blood test taken immediately before transfusion were also recorded.

3. Sample size

18 children studied pre- and post-transfusion allowed detection of differences before and after transfusion equivalent to one standard deviation of the results of each measurement technique with 80% power at the 5% level.

4. Analysis

The data were not normally distributed as assessed by the Pearson omnibus test, therefore, differences were assessed using Mann–Whitney U-tests. Spearman's correlations were calculated to determine the strength of relationships. Statistical analysis was performed using R software (version 3.1.1, R Foundation for Statistical Computing, Vienna, Austria).

5. RESULTS

Eighteen subjects with a median age of 14.2 (range 6.6-18.5) years were assessed, seven were female. Their median haemoglobin was 10.1 (range 8.2 – 11.6) g/dl and the median packed red cell volume (PRCV) administered was 500 (250 – 800) ml. Eight children (44%) had had at least one acute chest syndrome episode and four (22%) had a physician's diagnosis of asthma.

Prior to transfusion, their median TLC was 92.2 (71.6-135.1) % predicted for height, RV was 90.1 (61.7-104.3) % predicted for height and RV:TLC was 105.1 (87.4-134.8) % predicted for height. Six children had an obstructive (33%) and two (11%) a restrictive defect. Pulmonary capillary blood volume (Figure 1), Rrs5 (Figure 1), Rrs20, R5-R20, Xrs5, AX, D_LCO and KCO all increased after transfusion ($p < 0.0001$, $p < 0.0001$, $p = 0.0332$, $p = 0.0082$, $p = 0.0023$, $p = 0.0052$, $p < 0.0001$, $p < 0.0001$, respectively) (Table 1), whereas FEV₁, VC, and FEF₂₅₋₇₅ all declined ($p = 0.0056$, $p = 0.0008$, $p = 0.0483$ respectively) (Table 1). No significant change was seen in fres ($p = 0.0665$) or FEV₁/VC ($p = 0.2462$). The percentage change from baseline in pulmonary capillary blood volume correlated with the change in Rrs5 ($r = 0.50$, $p = 0.04933$), Rrs20 ($r = 0.60$, $p = 0.0091$) and KCO ($r = 0.58$, $p = 0.0265$), but not with R5-R20 ($r = 0.34$, $p = 0.1612$), FEV₁ ($r = -0.33$, $p = 0.0881$), VC ($r = -0.37$, $p = 0.1279$), FEF₂₅₋₇₅ ($r = 0.24$, $p = 0.0336$), FEV₁/VC ($r = 0.24$, $p = 0.3280$) or D_LCO ($r = 0.31$, $p = 0.1879$). The change in pulmonary capillary blood volume was correlated with the PRCV ($r = 0.56$, $p = 0.0152$).

6. DISCUSSION

We have demonstrated significant changes in lung function immediately following blood transfusion in children with SCD, increases in respiratory system resistance, reactance and gas transfer with decreases in FEV₁ and VC. Pulmonary capillary blood volume increased significantly and this change was correlated with changes in Rrs5, Rrs20 and KCO. VC also decreased, resulting in no significant change in FEV₁/VC.

Compared to healthy controls, children with SCD have an elevated cardiac output and pulmonary blood flow at rest, as well as raised pulmonary capillary blood volume as a result of chronic anaemia (Chaudry et al 2014, Wedderburn et al 2014). Our results suggest a link between increased pulmonary vascular volume and lung function abnormalities in SCD and that it is possible that respiratory symptoms reported in some children with SCD may

have been incorrectly attributed to asthma. It is important to emphasize that these results are not highlighting blood transfusions are inappropriate for SCD children, indeed the blood transfusions were associated with an increase in DLCO and KCO indicating improved gas exchange. Investigating lung function and capillary blood volume before and after blood transfusion has given a further means of investigating the association of respiratory mechanics, lung function abnormalities and pulmonary capillary blood volume.

This study has strengths and some limitations. The main strength of this study was the use of routine transfusion as a means of fluid loading (a treatment likely to alter pulmonary blood volume). This provided an 'experimental' model which allowed lung function to be assessed at different pulmonary capillary blood volumes, which would be inappropriate to do by other methods in SCD children and provided evidence of a possible relationship between elevated pulmonary capillary blood volume and lung function abnormalities. It is important to point out that the SCD children were in steady state and the impact of a transfusion may be different in an acutely unwell child with a sickle related episode. We measured the respiratory system resistance at 5Hz which is better able to capture total resistance to airflow, including changes in small airway function, than spirometry (Goldman et al 2005). These data were supported by the respiratory system resistance at 20Hz and frequency dependence of resistance, all of which increased significantly after transfusion. The low-frequency respiratory reactance parameters Xrs5 and AX also increased significantly, these parameters are thought at least in part to assess the elastic properties of the distal lung (Goldman et al 2005), it is, therefore, possible that the changes we observed related to changes in pulmonary compliance. The children who participated in the study were all undergoing regular transfusions as part of their clinical management. Such children are likely to suffer from more severe disease and may, therefore, be at greater risk of SCD-related vasculopathy (De Castro et al 2008, Duke et al 1964), which may have modulated their response to fluid loading. It would, however, be inappropriate to administer a fluid load

to an unselected cohort of SCD children. Post-transfusion haemoglobin levels were not available as the haemoglobin concentration takes approximately 24 hours to stabilise after transfusion. It was not possible, therefore, to correct the post-transfusion DLCO and KCO measurement for the haemoglobin level and so the uncorrected measurements were used. Caution must, therefore, be exercised in interpreting those results. A further limitation in the interpretation of our data is the lack of a control group, but it would not be appropriate to administer blood transfusions or intravenous fluids to healthy children. The respiratory system resistance and reactance results were related to reference ranges derived from Caucasian subjects (Nowowiejska et al 2008), but since the same reference range was used for both pre- and post-transfusion measurements, paired comparisons between them were valid.

7. CONCLUSIONS

In conclusion, this study has demonstrated that significant increases in pulmonary capillary blood volume and respiratory system resistance occur immediately following blood transfusion in children with SCD. Furthermore, the increase in respiratory system resistance significantly correlated with the increase in pulmonary capillary blood volume. These results provide evidence for a potential interaction between the increased pulmonary capillary blood volume and pulmonary function abnormalities seen in SCD children.

ACKNOWLEDGEMENTS

We thank Mrs Deirdre Gibbons for secretarial support.

Financial support: This research was supported by the National Institute for Health Research (NIHR) Biomedical Research Centre at Guy's and St Thomas' NHS Foundation Trust and King's College London. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

Conflict of interest: None to declare.

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Figure 1: Rrs5 and pulmonary capillary blood volume before and after transfusion.

Individual's data are shown by linked data points. Patients with spirometrically-defined obstructive defects at baseline are shown by dashed lines.

Table 1 Lung function and pulmonary capillary blood volume results before and after transfusion.

The results are expressed as median (range) and percent predicted for height except where indicated*. †Indicates absolute change.

	Pre-transfusion	Post-transfusion	%change from baseline*	P
Rrs5	127.4 (88.9-207.8)	141.3 (96.1-234.1)	10.7 (-3.6 - 22.0)	<0.0001
Rrs20	119.4 (78.2 – 187.5)	136.8 (80.5 – 191.9)	4.8 (-16.7 – 43.2)	0.0332
R5-R20* (kPa/l/s)	0.145 (0.00 – 0.420)	0.165 (0.01 – 0.541)	0.03 (-0.10- 0.29)†	0.0082
Xrs5	119.6 (49.7 – 201.0)	133.4 (65.0 – 281.2)	28.5 (-18.2- 69.8)	0.0023
f_{res}	112.7 (60.7 – 178.9)	118.7 (72.4 – 190.5)	6.3 (-21.1 – 49.0)	0.0665
AX* (kPa/L)	0.795 (0.05 – 3.820)	0.850 (0.13 – 5.130)	40.7 (-52.7- 200.0)	0.0052
FEV₁	84.4 (66.2-139.6)	79.4 (63.5-132.9)	-4.9 (-20.5 - 8.6)	0.0056
VC	94.2 (73.7-142.1)	90.72 (60.5-144.0)	-5.5 (-9.8 - 6.1)	0.0008
FEV₁:VC	91.2 (73.0-105.3)	92.7 (74.5-112.8)	2.6 (-12.0 – 17.5)	0.2462
FEF₂₅₋₇₅	69.9 (34.4-122.5)	62.5 (30.3-111.5)	-8.9 (-55.8 - 45.6)	0.0483
DLCO	74.8 (57.5-106.1)	90.2 (61.4-114.3)	12.0 (1.0 – 37.7)	<0.0001
KCO	71.1 (58.1-94.2)	90.4 (60.8-108.5)	19.2 (4.6 -49.1)	<0.0001

TLC	92.2 (71.6-135.1)	-		
RV	90.1 (61.7-104.3)	-		
RV:TLC	105.1 (87.4-134.8)	-		
DLCOc	88.3 (76.0-122.6)	-		
KCOc	86.8 (75.1-109.3)	-		
PCBV/BSA*	39.7 (25.3 – 63.6)	64.1 (33.4 – 129.3)	43.3 (14.1-108.2)	<0.0001
(ml/m²)				

Figure

